



**University of  
Zurich<sup>UZH</sup>**

**Zurich Open Repository and  
Archive**

University of Zurich  
University Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2014

---

## **Revisiting the impact of REM sleep behavior disorder on motor progression in Parkinson's disease**

Sommerauer, M ; Valko, P O ; Werth, E ; Poryazova, R ; Hauser, S ; Baumann, C R

**Abstract:** BACKGROUND Estimation of progression in Parkinson's disease (PD) is useful to guide clinical decisions and to enable patients to plan and manage their life with PD. Rapid eye movement (REM) sleep behavior disorder (RBD) and REM sleep without atonia (RWA) are recognized as early harbingers of neurodegeneration and may precede motor symptoms by years. However, their impact on motor progression remains elusive. METHODS We retrospectively analyzed polysomnographic and clinical data of 59 PD patients, grouping them into patients with RBD (n = 15), RWA (n = 22) and those with normal muscle atonia (n = 22). We compared the three groups with regard to motor progression, defined as changes in Unified Parkinson's Disease Rating Scale (UPDRS) III values per year, and selected PD specific characteristics. RESULTS Motor disability at first visit and time interval between first and last visits were similar between groups. We observed a significantly faster motor progression in PD patients with RBD and RWA than in those with preserved REM sleep atonia. CONCLUSION Our findings suggest that impaired muscle atonia during REM sleep might represent a marker of faster motor progression in PD.

DOI: <https://doi.org/10.1016/j.parkreldis.2014.01.005>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-100377>

Journal Article

Accepted Version

Originally published at:

Sommerauer, M; Valko, P O; Werth, E; Poryazova, R; Hauser, S; Baumann, C R (2014). Revisiting the impact of REM sleep behavior disorder on motor progression in Parkinson's disease. *Parkinsonism Related Disorders*, 20(4):460-462.

DOI: <https://doi.org/10.1016/j.parkreldis.2014.01.005>

# Revisiting the impact of REM sleep behavior disorder on motor progression ~~of~~ in Parkinson's disease

Michael Sommerauer, Philipp O. Valko, Esther Werth, Rositsa Poryazova,

Sabrina Hauser, Christian R. Baumann

Department of Neurology, UniversitätsSpital Zurich, Zurich, Switzerland.

\*Corresponding address Michael Sommerauer  
Department of Neurology  
University Hospital Zurich  
Frauenklinikstrasse 26  
CH-8091 Zurich  
Phone: +41 44 255 55 11  
michael.sommerauer@usz.ch

Character count (title)	<del>9690</del>
Word count (abstract)	180
Word count	<del>1281</del> 1052
Figures / Tables	2
References	<del>14</del> 12

Running title Revisiting RBD

Keywords REM sleep behaviour disorder, REM sleep without atonia, disease progression, Parkinson's disease

Conflict of Interest The authors declare that there is no conflict of interest regarding this work.

Funding source No funding was acquired for this work.

## Abstract

**Background:** Estimation of progression in Parkinson's disease (PD) is useful to guide clinical decisions and to enable patients to plan and manage their life with PD. Rapid eye movement (REM) sleep behavior disorder (RBD) and REM sleep without atonia (RWA) are recognized as early harbingers of neurodegeneration and may precede motor symptoms by years. However, their impact on motor progression remains elusive.

**Methods:** We retrospectively analyzed polysomnographic and clinical data of 59 PD patients, grouping them into patients with RBD (n=15), RWA (n=22) and those with normal muscle atonia (n=22). We compared the three groups with regard to motor progression, defined as changes in Unified Parkinson's Disease Rating Scale (UPDRS) III values per year, and selected PD specific characteristics.

**Results:** Motor disability at first visit and time interval between first and last visits were similar between groups. We observed a significantly faster motor progression in PD patients with RBD and RWA than in those with preserved REM sleep atonia.

**Conclusion:** Our findings suggest that impaired muscle atonia during REM sleep might represent a marker of faster motor progression in PD.

## Introduction

Several prognostic factors including postural instability, predominance of type and body side of motor features at disease onset impact the evolution of motor and non-motor symptoms in Parkinson's disease (PD) [1-4]. In the first description of REM sleep behavior disorder (RBD) by Schenck et al. in 1986, a close link to neurodegenerative disorders was already reported [5]. RBD consists of two features: loss of atonia during REM sleep, so called REM sleep without atonia (RWA) and acting out of dreams, most often of violent content [6]. In this line, it would be important to know whether RBD and RWA not only heralds the occurrence of PD [7], but also predicts the pace of disease progression. As RBD is associated with higher doses of levodopa, occurrence of hallucinations and higher burden of autonomic failure [8], RBD may reflect a more widespread neurodegeneration. Still, longitudinal studies to examine the association between RBD and PD progression are rare. Only one study investigated the predictive value of RBD on motor disability in PD over time [9]. Thirty-nine PD patients with interview-based diagnoses of RBD were compared to 22 PD patients without RBD, and significantly faster evolution of motor disability or of several non-motor symptoms was not found [9]. Therefore, our goal was to analyze the influence of polysomnography (PSG)-proven RBD and REM sleep without atonia (RWA) on progression of motor disability.

## Methods

We retrospectively analysed 104 consecutive PD patients of our outpatient movement disorder unit who underwent video-polysomnography (PSG) from 2003-2010 for diagnostic purposes (i.e. for the assessment of RBD, sleep apnea, or periodic limb movements).—We excluded patients with deep brain stimulation (n=4), incomplete follow-up data (n=38) and no REM sleep in PSG (n=3). All patients accepted to provide their data for research purposes by written informed consent; ethical approval for retrospective analyses was waived.

Clinical information included disease type (i.e. tremor-dominant vs. akinetic-rigid phenotype or equal distribution [2]), predominantly affected body side, motor disability and disease severity as measured by UPDRS part III on medication (during outpatient visits) and Hoehn

& Yahr scale, respectively, and calculation of total levodopa equivalent doses (LED) [10]. Polysomnographic diagnosis of RBD and RWA was performed along international recommendations [11]: We used following references values: a 30-second epoch was scored as tonic if chin EMG activity was present for more than 50% of the epoch; phasic epochs were scored in response of 2-second mini-epochs (within 30-second REM sleep epoch) with bursts of EMG activity; RWA was ascertained if tonic chin EMG density was greater than approximately 30% and / or a phasic chin EMG density was greater than approximately 15% of total REM sleep time ~~was assessed as REM sleep without atonia (RWA)~~. RWA with complex movements or vocalization as assessed by time-locked video was defined as manifest RBD. All patients exhibiting one or more episodes with RBD during PSG were here defined as patients with RBD; patients with REM sleep atonia abnormalities but without any episode of complex movements or vocalization were classified as patients with RWA.

We used SPSS (version 21) for statistical analyses. Motor progression was calculated as difference of UPDRS III values between first and last visits, divided by the number of years between these visits [2]. To calculate differences between groups, we applied one-way ANOVA with trend analysis on significant results or Kruskal-Wallis tests for multiple groups, Student's t-test or Mann-Whitney tests for two groups, and Chi-Square tests when appropriate. Trend analysis was performed with -1.5, 0.5 and 1 as coefficients to enhance differentiation between preserved REM atonia to any type of altered REM sleep tonus and to include all three groups. Stepwise multiple linear regression analysis was performed for multivariate analysis (dependent variable: total change of UPDRS III per year; independent variables: REM sleep tonus (preserved, RWA or, RBD), sex, age, age at onset, predominant side and motor type of symptoms, disease duration, Hoehn & Yahr scale, UPDRS III, length of interval between first and last visit, change of total LED per year, and total LED at baseline).

## Results

Demographics, disease duration, motor disability and dopaminergic treatment were similar in PD patients with RBD, RWA and preserved REM atonia (Table 1). While UPDRS III scores at first visit were similar, group comparisons revealed significant differences in motor progression after mean follow-up of  $2.5 \pm 1.5$  years, with most pronounced decline of motor function in PD patients with RBD, intermediate decline in those with RWA and almost no deterioration in those with preserved REM atonia (Figure 1). Trend analysis revealed a significant trend on UPDRS III at last visit and on motor progression per year from preserved REM atonia to RWA to RBD ( $p = 0.015$  and  $p = 0.014$ , respectively). Similarly, linear regression analysis confirmed that presence of RBD or RWA was strongly associated with UPDRS III increment ( $\beta = 0.302$ ,  $p = 0.015$ , co-associate: change of total LED per year:  $\beta = 0.263$ ,  $p = 0.003$ ).

When analyzing only two groups, i.e. those patients with RWA or RBD against those with normal REM, this finding did not change (Table 1). In linear regression analysis, incidence of altered REM sleep tonus was again the strongest associate with total change of UPDRS III per year ( $\beta = 0.302$ ,  $p = 0.015$ , co-associates: age:  $\beta = 0.244$ ,  $p = 0.046$  and change of total LED per year:  $\beta = 0.282$ ,  $p = 0.023$ ).

## Discussion

Our study in 59 PD patients suggests that both RWA and RBD predict faster deterioration of motor function. Our results are not in accordance with the earlier report of Lavault et al. [9]. Both studies included similar numbers of patients, but RBD was differently assessed: by history in the previous study, and by video-polysomnography in this report. In our analysis, patients with RWA elicit a faster motor worsening. As altered REM sleep in patients with RWA is not detected as in an interview based study, differences in classification may explain the divergent outcomes in these two studies.

The observed disparity of motor progression is difficult to explain, because the neuroanatomical substrates for loss of REM atonia and motor symptoms in PD do not

overlap. Animal studies and few observations in humans indicate that the locus subcoeruleus ~~sublaterodorsal nucleus, the precoeruleus complex~~ and the magnocellular reticular formation regulate atonia in REM sleep [13], while dysfunction of basal ganglia circuitries is believed to underlie motor problems in PD. Thus, RBD and RWA might reflect more widespread, more pronounced alpha-synuclein neuropathology in terms of a propagation of adjacent brainstem nuclei [7].

Our study has several limitations. First of all, the number of included patients is low and follow-up times were rather short. Still, despite these quantitative limitations, the finding of accelerated progression in REM-altered PD patients was significant. Furthermore, the setting was retrospective, and indication for PSG was done on clinical purpose. Thus, UPDRS III examinations off and on medication were not performed, and an inclusion bias cannot be ruled out. The use of additional limb EMG instead of chin EMG only would be more accurate to detect RWA [13]; however, due to the retrospective design of our study, it was not available in all patients. We only performed one night of PSG which might impair the detection rate of dream enactment during RWA to define RBD as there is a considerable inter-night variance in RBD [14]. We therefore also performed statistical analysis of only two groups (with and without REM sleep tonus abnormalities) which revealed similar results. Nevertheless, positive trend analysis points to a significant difference between ~~solely~~ RWA and manifest RBD concerning motor progression in PD. This should, however, be confirmed by larger studies. –Altogether, for a definite answer whether or not RBD impacts motor progression, the best of the 2 studies should be combined in a new study, particularly with a prospective setting in a larger number of patients, longer follow-up intervals, measurements of UPDRS III in the off state and of RWA/RBD by polysomnography with additional limb EMG, and maybe even nuclear medicine measurements as marker of neurodegeneration could be considered.

## References

- [1] Tomer R, Levin BE, Weiner WJ. Side of onset of motor symptoms influences cognition in Parkinson's disease. *Ann Neurol* 1993;34:579-84.
- [2] Baumann C, Held U, Valko P, Wienecke M, Waldvogel D. Body side and predominant motor features at the onset of Parkinson's disease are linked to motor and non-motor progression. *Mov Disord* 2013; in press.
- [3] Post B, Merkus MP, de Haan RJ, Speelman JD. Prognostic factors for the progression of Parkinson's disease: a systematic review. *Mov Disord* 2007;22:1839-51.
- [4] Marras C, Rochon P, Lang AE. Predicting motor decline and disability in Parkinson disease: a systematic review. *Arch Neurol* 2002;59:1724-8.
- [5] Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep* 1986;9:293-308.
- [6] Arnulf I. REM sleep behavior disorder: motor manifestations and pathophysiology. *Mov Disord* 2012;27:677-89.
- [7] Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valdeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol* 2013;12:443-53.
- [8] Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. *J Neurol Neurosurg Psychiatry* 2008;79:387-91.
- [9] Lavault S, Leu-Semenescu S, Tezenas du Montcel S, Cochen de Cock V, Vidailhet M, Arnulf I. Does clinical rapid eye movement behavior disorder predict worse outcomes in Parkinson's disease? *J Neurol* 2010;257:1154-9.



[10] Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. [Mov Disord](#) 2010;25:2649-53.

Formatiert: Französisch (Schweiz)

[11] Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. [Mov Disord](#) 2010;25:2044-51.

[12] Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. [Brain](#) 2007;130:2770-88.

[\[13\] Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. \[Sleep\]\(#\). 2012;35:835-47.](#)

[\[14\] Zhang J, Lam SP, Ho CK, Li AM, Tsoh J, Mok V, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? \[Sleep\]\(#\). 2008;31:1179-85.](#)

**Table 1**

Demographic and clinical characteristics of 59 patients with Parkinson's disease, grouped according to abnormalities of REM sleep muscle tone. RBD=REM sleep behaviour disorder. RWA=REM sleep without atonia. UPDRS=Unified Parkinson's Disease Rating Scale. LED=Levodopa equivalent dose.

	<b>Preserved REM atonia</b>	<b>RWA</b>	<b>RBD</b>	<b>p</b>	<b>RWA or RBD</b>	<b>p</b>
<i>n</i>	15	22	22		44	
<b>Sex, female (%)</b>	47	46	46	ns	46	ns
<b>Age (years)</b>	66±11	64±10	69±5	ns	67±8	ns
<b>Disease duration years</b>	7.5 ± 6.0	8.4 ± 6.7	9.7 ± 6.8	ns	9.1 ± 6.7	ns
<b>Hoehn &amp; Yahr (mean)</b>	2.2 ± 0.7	2.4 ± 0.8	2.4 ± 1.0	ns	2.4 ± 0.9	ns
<b>Left side more affected (%)</b>	53	72	50	ns	61	ns
<b>Tremor-dominant PD (%)</b>	33	27	36	ns	32	ns
<b>First visit:</b>						
<b>UPDRS III (mean)</b>	21± 6	20±7	21±8	ns	21±7	ns
<b>Dyskinesia (%)</b>	14	41	41	ns	41	ns
<b>Total LED (mg/d)</b>	652±532	753±465	798±363	ns	776±415	ns
<b>Last visit:</b>						
<b>Interval first-last visit (years)</b>	2.1±1.0	2.7±1.9	2.7±1.2	ns	2.7±1.6	ns
<b>UPDRS III (mean)</b>	22±7	26±10	32±10	<b>0.016</b>	29±10	<b>0.034</b>
<b>Total LED (mg/d)</b>	730±437	826± 434	886±410	ns	856±418	ns
<b>Motor progression:</b>						
<b>UPDRS III / year (mean)</b>	0.1±3.6	3.0±5.6	4.3±4.9	<b>0.04</b>	3.7±5.2	<b>0.018</b>

## Figure 1

Accelerated motor decline in patients with Parkinson's disease with REM sleep tonus abnormalities. RBD=REM sleep behaviour disorder. RWA=REM sleep without atonia. UPDRS=Unified Parkinson's Disease Rating Scale. \*= $p<0.05$  for group comparison.